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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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SALIWANCHIK LLOYD & SALIWANCHIK
A PROFESSIONAL ASSOCIATION
2421 N.W. 41ST STREET
SUITE A-1
GAINESVILLE, FL 326066669

EXAMINER

KRUSE, DAVID H

ART UNIT

PAPER NUMBER

1638

DATE MAILED: 05/06/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary

Application No.

09/918,740

Applicant(s)

HAHN ET AL.

Examiner

David H Kruse

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
 Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12/3/02 & 2/21/03.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-114 is/are pending in the application.
- 4a) Of the above claim(s) 1-15, 21-55 and 57-114 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 16-20 and 56 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 31 July 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
 If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) ☐ All b) ☐ Some * c) ☐ None of:
 1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
 a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5&6. 6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group V, claims 16-20 and 55-65, in Paper No. 9, and SEQ ID NO: 59, in Paper No. 11, is acknowledged.
2. Claims 1-15, 21-54 and 66-114 are withdrawn from further consideration pursuant to 37 CFR § 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. In addition, claims 55 and 57-65 are withdrawn from consideration as directed to nonelected nucleotide sequences in Paper No 11. Election was made **without** traverse in Paper Nos. 9 and 11.
3. This application contains claims 1-15, 21-55 and 57-114 drawn to an invention nonelected with traverse in Paper Nos. 9 and 11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR § 1.144). See MPEP § 821.01.
4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR § 1.48(b) and by the fee required under 37 CFR § 1.17(i).

Information Disclosure Statement

5. The information disclosure statement filed 28 January 2002 fails to comply with 37 CFR § 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent;

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each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been considered in part because reference AS on page 8 was not enclosed and the information is not sufficient for the Examiner to procure a copy of the information, said reference will not be printed on the face of the issued patent. A signed copy of the IDS filed 28 January 2002 and 28 February 2002 is attached hereto.

Specification

6. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 22, line 11. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 16-20 and 55 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicant claims a method for providing transformed cells having increased isoprenoid production as compared to non-transformed cells comprising providing an

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isolated polynucleotide comprising polynucleotide sequences encoding the enzymes of the complete mevalonate pathway.

Applicant teaches polynucleotide constructs comprising polynucleotide sequences encoding enzymes in the mevalonate pathway, and that polynucleotides from various organisms have been isolated that encodes the enzymes of the mevalonate pathway (see SEQ ID NO: 59 and pages 18-19 of the specification). Applicant provides prophetic guidance for the claimed method in *E. coli*, and plants (pages 50-58 of the specification).

Applicant does not reduce to practice the claimed method, and does not provide guidance for the claimed method in any cell as broadly claimed (in particular claims 16, 17 and 56).

In re Wands, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight considerations for determining whether or not undue experimentation would be necessary to practice an invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Applicant has provided guidance only for how to construct polynucleotides comprising polynucleotide sequences encoding the enzymes of the complete mevalonate pathway. Applicant provides only general guidance for how to practice the claimed method of increasing isoprenoid production as compared to non-transformed

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cells in the instant specification. The art teaches that the nature of the invention requires extensive guidance in order to practice the claimed method, especially in plants. Herbers *et al* (1996, TIBTECH 14:198-205) teach that it is generally accepted that metabolic control is a function of many enzymes in a pathway and is not due to single rate-limiting steps and that metabolic configurations in transgenic plant will only be beneficial as long as the cellular constituents required for plant growth and survival are not seriously affected (see page 198, right column).

The mevalonate pathway is recognized in the art as comprising the six enzymes acetoacetyl-CoA synthase (A), HMG-CoA synthase (B), HMG-CoA reductase (C), MVA kinase (D), PMVA kinase (E), and DPMVA decarboxylase (F), leading to the production of isopentenyl diphosphate (Takagi *et al* 2000, J. Bact. 182(15):4153-4157, see page 4153, left column). Claims 16, 17 and 56 are directed to a method in any target cell and claims 18-20 are directed to a method in a plant cell. The art teaches that overexpression of HMG-CoA reductase, enzyme (C), does lead to an increase in the accumulation of total sterols however the accumulation of normal end-product sterols is not influences to the same extent as the accumulation of intermediates and that increases in the production of isoprenoids such as carotenoids, tocopherol and sesquiterpenes did not occur (Chappell *et al* 1995, Plant Physiology 109:1337-1343, see pages 1241-1342). Re *et al* (1995, The Plant Journal 7(5):771-784) teach that co-expression of native and introduced genes of HMG-CoA reductase resulted in elevated mRNA levels but only modest increases in enzyme activity and largely unchanged isoprenoid biosynthesis, suggesting that regulation occurs at multiple levels in plants as

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well as in animals (Summary on page 771, and page 780, left column, 2nd paragraph).

Lluch *et al* (2000, Plant Molecular Biology 42: 365-376) teach that MVA kinase from eukaryotic organisms, enzyme (D), is regulated by feedback inhibition by prenyl diphosphates of different lengths and that in mammals the enzyme is subject to regulation at the transcriptional level in response to sterol levels (see page 366 and 373). Cordier *et al* (1999, Plant Molecular Biology 39:953-967) teach that attempts to complement the *erg19* mutation of *S. cerevisiae* did not lead to expected results using an *A. thaliana* cDNA encoding DPMVA decarboxylase, enzyme (F), and that the plant enzyme appeared to have a lower specific activity in yeast, and did not function comparably as in the plant (pages 965-966).

The instant claims are directed to a method using a polycistronic polynucleotide, claims 18-20 being specifically directed to a method in plants. The art teaches that expression of polycistronic polynucleotide sequences in plants is not a predictable art because in plant, as well as animals, mRNAs are translated monocistronically, the exception being some chloroplast genes, and that premature translation termination and decreased mRNA stability must be addressed in expressing polycistronic polynucleotides in plants (Cho *et al* 1995, J Ferment. Bioengin. 80(2):111-117, see pages 111 and 116).

Given the limited guidance by Applicant, the lack of evidence of reduction to practice of the claimed method, the nature of the claimed method and the teaching of the art concerning regulation of the mevalonate pathway and expression of polycistronic polynucleotides in plants and animals, it would have required undue trial and error

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experimentation by one of skill in the art at the time of Applicant's invention to screen through a myriad of polynucleotides comprising polynucleotide sequences encoding the enzymes of the complete mevalonate pathway, even comprising the polynucleotide sequence of SEQ ID NO: 59, and transform a myriad of target cells, including microalgae or other plant cells, and identify those polynucleotides that could be used in the claimed method to increase isoprenoid production as compared to non-transformed cells as claimed. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970) which teaches "That paragraph (35 USC 112, first) requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.". In the instant case, a method of providing transformed cells having increased isoprenoid production comprising providing an isolated polynucleotide comprising polynucleotide sequences encoding the enzymes of the complete mevalonate pathway is highly unpredictable without empirical evidence to the contrary.

9. The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

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10. Claims 17 and 20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 17 is indefinite because at line 2 the phrase "the polynucleotide sequence encoding IPP isomerase" appears to be directed to a specific sequence for which there is no antecedent basis in claim 16. Hence, it is unclear what the metes and bounds of the claim are.

At claim 20, line 2, the phrase "transformed plant" is indefinite because "plant" lacks antecedent basis in claim 16, and there is no indication of providing a target plant cell in claim 16, hence it is unclear how one gets a transformed plant from any target cell.

Conclusion


11. The claims are free of the prior art which neither teaches nor suggests providing transformed cells having increased isoprenoid production comprising providing an isolated polynucleotide comprising polynucleotide sequences encoding the enzymes of the complete mevalonate pathway.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David H. Kruse, Ph.D. whose telephone number is (703) 306-4539. The examiner can normally be reached on Monday to Friday from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy Nelson can be reached at (703) 306-3218. The fax telephone number for this Group is (703) 872-9306 Before Final or (703) 872-9307 After Final.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group Receptionist whose telephone number is (703) 308-0196.



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David H. Kruse, Ph.D.
5 May 2003